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=> s excessive apoptosis
L1 753 EXCESSIVE APOPTOSIS

=> s l1 and blood
L2 163 L1 AND BLOOD

=> s l2 and detection
L3 10 L2 AND DETECTION

=> dup remove l3
PROCESSING COMPLETED FOR L3
L4 6 DUP REMOVE L3 (4 DUPLICATES REMOVED)

=> s l4 and anti-nucleolin
L5 1 L4 AND ANTI-NUCLEOLIN

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN
2004:20982 Document No. 140:90312 A method for the **detection** of
apoptosis via determination of nucleolin and/or PARP-1 in the sample.
Bates, Paula J.; Mi, Yingchang (University of Louisville Research

Foundation, Inc., USA). PCT Int. Appl. WO 2004003554 A1 20040108, 66 pp.
DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN,
YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ,
CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2003-US20167 20030626. PRIORITY: US 2002-392143P
20020626.

AB Methods for the **detection** of apoptosis by measuring apoptotic
bodies shed by apoptotic cells are provided, as are kits to carry out such
methods. The method comprises preparing a sample from which cells have been
removed and determining at least one of nucleolin and PARP-1 in the sample.

The **detection** of either (or both) compds. comprises the
detection of a nucleolin (PARP-1)-binding mol.-nucleolin (PARP-1)
complex. The binding mols. are **anti-nucleolin**
(anti-PARP-1) antibodies and for nucleolin also guanosine-rich
oligonucleotides. The sample can be **blood**, serum, plasma,
tissue, tissue culture medium, or sputum. The method can be used to determine
excessive apoptosis via preparing a **blood** sample
from a subject suspected of having a disease selected from the group
consisting of AIDS, neurodegenerative disease, ischemic injury, autoimmune
disease, tumor, cancer, viral infection, acute inflammation, and sepsis.

=> s 14 and anti-PARP
L6 1 L4 AND ANTI-PARP

=> d 16 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN
2004:20982 Document No. 140:90312 A method for the **detection** of
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Bates, Paula J.; Mi, Yingchang (University of Louisville Research
Foundation, Inc., USA). PCT Int. Appl. WO 2004003554 A1 20040108, 66 pp.
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CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN,
YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ,
CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC,
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from a subject suspected of having a disease selected from the group
consisting of AIDS, neurodegenerative disease, ischemic injury, autoimmune
disease, tumor, cancer, viral infection, acute inflammation, and sepsis.

=> dup remove l3
PROCESSING COMPLETED FOR L3
L7 6 DUP REMOVE L3 (4 DUPLICATES REMOVED)

=> s l7 and pd<20020602
2 FILES SEARCHED...
L8 5 L7 AND PD<20020602

=> d l8 1-5 cbib abs

L8 ANSWER 1 OF 5 MEDLINE on STN
2000009430. PubMed ID: 10541822. Technetium-99m HYNIC-annexin V: a potential radiopharmaceutical for the in-vivo **detection** of apoptosis. Ohtsuki K; Akashi K; Aoka Y; Blankenberg F G; Kopiwoda S; Tait J F; Strauss H W. (Division of Nuclear Medicine, Department of Radiology, Stanford University Medical Center, Stanford, CA 94305, USA.) European journal of nuclear medicine, (1999 Oct) Vol. 26, No. 10, pp. 1251-8. Journal code: 7606882. ISSN: 0340-6997. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Either inadequate or **excessive apoptosis** (programmed cell death) is associated with many diseases. A method to image apoptosis in vivo, rather than requiring histologic evaluation of tissue, could assist with therapeutic decision making in these disorders. Programmed cell death is associated with a well-choreographed series of events resulting in the cessation of normal cell function, and the ultimate disappearance of the cell. One component of apoptosis is signaling adjacent cells that this cell is committing suicide by externalizing phosphatidylserine to the outer leaflet of the cell membrane. Annexin V, a 32-kDa endogenous human protein, has a high affinity for membrane-bound phosphatidylserine. We have coupled annexin V with the bifunctional hydrazinonicotinamide reagent (HYNIC) to prepare technetium-99m HYNIC-annexin V and demonstrated localization of radioactivity in tissues undergoing apoptosis in vivo. In this report we describe the results of a series of experiments in mice and rats to characterize the biologic behavior of (99m)Tc-HYNIC-annexin V. Biodistribution studies were performed in groups of rats at 10-180 min after intravenous injection of (99m)Tc-HYNIC-annexin V. In order to estimate the degree of apoptosis required for localization of (99m)Tc-annexin V in vivo, mice were treated with dexamethasone at doses ranging from 1 to 20 mg/kg, 5 h prior to (99m)Tc-HYNIC-annexin V administration, to induce thymic apoptosis. Thymus was excised 1 h after radiolabeled HYNIC-annexin V injection; thymocytes were isolated, incubated with Hoechst 33342 followed by propidium iodide, and analyzed on a fluorescence-activated cell sorter. Each sorted cell population was counted in a scintillation counter. To test (99m)Tc-HYNIC-annexin V as a tracer for external radionuclide imaging of apoptotic cell death, radionuclide imaging of Fas-defective mice (lpr/lpr mice) and wild-type mice treated with the antibody to Fas (anti-Fas) was carried out 1 h post injection. Rat biodistribution studies demonstrated a **blood** clearance half-time of less than 10 min for (99m)Tc-HYNIC-annexin V. The kidneys had the highest concentration of radioactivity at all time points. Studies in the mouse thymus demonstrated a 40-fold increase in (99m)Tc-HYNIC-annexin V concentration in apoptotic thymocytes compared with the viable cell population. A correlation of $r=0.78$ was found between radioactivity and flow cytometric and histologic evidence of apoptosis. Imaging studies in the lpr/lpr and wild-type mice showed a substantial increase of activity in the liver of wild-type mice treated with anti-Fas, while there was no significant change, irrespective of anti-Fas administration, in lpr/lpr mice. Excellent images of hepatic apoptosis were obtained in wild-type mice 30 min after injection of (99m)Tc-HYNIC-annexin V. The imaging results were consistent with histologic analysis in these animals. In conclusion, these studies confirm the value of (99m)Tc-HYNIC-annexin V uptake as a marker for the **detection** and quantification of apoptotic cells in vivo.

L8 ANSWER 2 OF 5 MEDLINE on STN

1998447466. PubMed ID: 9776571. A cytofluorometric method for the simultaneous **detection** of both intracellular and surface antigens of apoptotic peripheral lymphocytes. Lecoeur H; Ledru E; Gougeon M L. (Unite d'Oncologie Virale, Departement SIDA et Retrovirus, Institut Pasteur, Paris, France.) Journal of immunological methods, (1998 Aug 1) Vol. 217, No. 1-2, pp. 11-26. Journal code: 1305440. ISSN: 0022-1759. Pub. country: Netherlands. Language: English.

AB The aim of this study was to define a simple and reliable method to detect simultaneously surface and intracellular antigens in apoptotic peripheral human lymphocytes. This approach requires a permeabilizing procedure for intracellular access of mAbs, which raises the important question of the influence of this procedure on parameters which identify apoptotic cells and on the surface expression of antigens. We compared the effects of three currently used permeabilizing methods (saponin quillaia bark 0.05%, Triton X-100 0.1, ethanol 70%) on the quantification of apoptotic lymphocytes, defined according to FSC/SSC criteria or following 7-AAD staining, and on the **detection** of surface CD3, CD4, CD8, Fas, CD45RO molecules. The combined **detection** of these surface antigens with intracellular molecules, including Bcl-2 and cytokines (IFNgamma, TNFalpha, IL-2) was also analysed in the context of these three permeabilizing procedures. All the experiments were performed on PBMC from HIV-infected donors, known to undergo **excessive apoptosis** following short-term culture. We report that permeabilization with saponin is the only procedure which allows: (1) the preservation of lymphocyte morphology determined by the FSC/SSC parameters; (2) the quantification of apoptotic lymphocytes following 7-AAD staining; (3) a reliable surface immunophenotyping, maintaining a good antibody binding capacity (ABC); (4) the proper **detection** of intracellular membrane bound antigens (Bcl-2) and intracellular cytokines (IFNgamma, TNFalpha, IL-2); (5) the combined **detection** of apoptotic nuclei, surface antigens and intracellular molecules. Altogether these observations demonstrate that the simultaneous analysis of extracellular and intracellular antigens in apoptotic cells belonging to a complex lymphoid populations such as PBMC can be readily overcome provided the detergent used for cell permeabilization is appropriate and the successive staining procedures performed in a defined order.

L8 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2001:297545 Document No.: PREV200100297545. Biologic determinants of clinical response to Thalidomide in myelodysplasia. Mundle, S. [Reprint author]; Zorat, F. [Reprint author]; Shetty, V. [Reprint author]; Allampallam, K. [Reprint author]; Alvi, S. [Reprint author]; Lisak, L. [Reprint author]; Little, L. [Reprint author]; Dean, L. [Reprint author]; Nascimben, F. [Reprint author]; Ekbal, M. [Reprint author]; duRandt, M. [Reprint author]; Broderick, E. [Reprint author]; Venugopal, P. [Reprint author]; Raza, A. [Reprint author]. Rush Cancer Institute, Rush-Presbyterian-St. Luke's Medical Center (RPSLMC), Chicago, IL, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 146a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Based on the earlier observations of increased levels of tumor necrosis factor alpha (TNFalpha) and **excessive apoptosis** in the bone marrow (BM) of patients with myelodysplastic syndromes (MDS), a suppressor of TNFalpha; Thalidomide, was used in the therapy of MDS at our center on a protocol approved by the IRB of RPSLMC. Thalidomide was administered at an initial total daily oral dose of 100mg po increased to 400mg as tolerated. Thirty-one patients (Refractory anemia (RA)- 18, RA with ringed sideroblasts (RARS)- 6, RA with excess blasts (RAEB)-6 and Chronic myelomonocytic leukemia (CMML)-1) completed 12 weeks of therapy. Significant hematological responses were noted in 16 patients (11/18 RA and 5/6 RARS). In order to determine the biologic correlates of these responses, patients' sera were assessed by ELISA for the levels of

TNFalpha, transforming growth factor beta (TGFbeta), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Additionally, plastic embedded bone marrow biopsy sections were examined for the extent of apoptosis by in situ end labeling (ISEL) and for the presence of TNFalpha, and TGFbeta by immunohistochemistry using a subjective rating scale of 1+ to 8+. In the sera of both responders (R) and non-responders (NR) the VEGF levels correlated positively with TGFbeta and TNFalpha levels. Interestingly, a significant correlation was seen with bFGF ($r=0.679$, $p=0.04$) only in NR. Also, while VEGF correlated negatively with hemoglobin (Hgb) levels in this group ($r: -0.8$, $p=0.03$), demonstrated a positive correlation with Hgb in R group ($r=0.609$, $p=0.058$). Surprisingly, in the R group, BM biopsies showed significantly lower median levels of apoptosis, TGFbeta and TNFalpha, (1+, $p=0.19$; 1+, $p=0.012$, and 2+, $p=0.04$ respectively), as compared to those in the NR group (4.5+, 6+ and 3+ respectively). Clearly, patients with low cytokine and apoptosis levels appear to benefit from the treatment with Thalidomide. This constitutes a biologically recognizable subgroup of good-risk patients who are likely to respond to manipulations of cytokine pathways. The precise mechanism of Thalidomide activity in MDS remains obscure is most likely a result of its anti-angiogenic, anti-cytokine and immunomodulatory effects.

L8 ANSWER 4 OF 5 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

2002:5996 The Genuine Article (R) Number: 502ZQ. Contributions of flow cytometry to the analysis of the myelodysplastic syndrome. Miller D T (Reprint); Stelzer G T. Esoterix Oncol, Flow Cytometry Lab, 210 Summit View Dr, Suite 100, Brentwood, TN 37027 USA (Reprint); Esoterix Oncol, Flow Cytometry Lab, Brentwood, TN 37027 USA; Esoterix, Austin, TX USA. CLINICS IN LABORATORY MEDICINE (DEC 2001) Vol. 21, No. 4, pp. 811-+. ISSN: 0272-2712. Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Epidemiologic survey instruments need to be put in place to document changes in the incidence of myelodysplastic syndrome (MDS). Cytogenic abnormalities have not provided an explanation of MDS but are of diagnostic and prognostic significance. The emergence of immunologic factors is of major importance and emphasizes the need for early **detection**. Flow cytometry can be used diagnostically to exclude other causes of cytopenias, document the phenotypic manifestations of myeloid dysmaturation, and provide blast enumeration. There is a need for continued work to establish minimal diagnostic criteria for MDS. The current prognostic scoring systems do not incorporate findings from the newer technologies.

L8 ANSWER 5 OF 5 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

1999:36948 The Genuine Article (R) Number: 153LK. 'Low-risk' myelodysplastic syndrome is associated with **excessive apoptosis** and an increased ratio of pro-versus anti-apoptotic bcl-2-related proteins. Parker J E; Fishlock K L; Mijovic A; Czepulkowski B; Pagliuca A; Mufti G J (Reprint). Kings Coll Hosp & Sch Med & Dent, Dept Haematol, Bessemer Rd, London SE5 9RS, England (Reprint); Kings Coll Hosp & Sch Med & Dent, Dept Haematol, London SE5 9RS, England. BRITISH JOURNAL OF HAEMATOLOGY (DEC 1998) Vol. 103, No. 4, pp. 1075-1082. ISSN: 0007-1048. Publisher: BLACKWELL SCIENCE LTD, P O BOX 88, OSNEY MEAD, OXFORD OX2 ONE, OXON, ENGLAND. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We performed flow cytometric analysis of CD34(+) cell apoptosis in 59 patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) secondary to MDS (MDS-AML) using annexin V-FITC, which binds to exposed phosphatidylserine on apoptotic cells. Apoptosis was significantly increased in FAB subtypes RA, RARS and RAEB (<10% blasts) (56.5% (15.1-86.5%)) compared to normal controls (18.5% (3.4-33.4%)),

P<0.0001) and RAEBt/MDS-AML (16% (2.1-43.2%), P<0.0001). There was no correlation between % apoptosis, Full blood count or cytogenetics in any disease category. Two-colour cytometric analysis of permeabilized CD34(+) cells stained with antibodies to Bcl-2, Bcl-X (anti-apoptotic), Bax and Bad (proapoptotic), demonstrated significantly higher ratios of pro- v anti-apoptotic proteins in early MDS (2.47 (1.19-9.42) compared to advanced disease (1.14 (0.06-3.32), P = 0.0001). Moreover, using repeated measures of variants (ANOVA), we found that variations between individual Bcl-2-related proteins differed significantly according to disease subtype (P<0.0005). Our results confirm that CD34(+) cell apoptosis was significantly increased in MDS subtypes RA and RARS and fell with disease progression. Early MDS was also associated with a significantly higher CD34(+) cell pro-v anti-apoptotic Bcl-2-family-protein ratio than advanced disease. Furthermore, patterns of expression of individual Bcl-2 related proteins differed significantly between different disease categories. However no correlation between pro-v anti-apoptotic Bcl-2-family-protein ratios and the degree of apoptosis was observed.

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=> s l2 and acquired immunodeficiency syndrome
L9          0 L2 AND ACQUIRED IMMUNODEFICIENCY SYNDROME
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=> s l2 and AIDS
L10         3 L2 AND AIDS
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L11         3 DUP REMOVE L10 (0 DUPLICATES REMOVED)
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L12         2 L11 AND PD<20020602
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=> d l12 1-2 cbib abs
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L12 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
2002:327025 Document No.: PREV200200327025. Programmed cell death and its
clinical implications. Katoch, Bandhana; Sebastian, Sonia; Sahdev, Sudhir;
Padh, Harish; Hasnain, Seyed E.; Begum, Rasheedunnisa [Reprint author].
Department of Biochemistry, M. S. University of Baroda, Vadodara, 390 002,
India. rasheeda@wilnetonline.net. Indian Journal of Experimental Biology,
(May, 2002) Vol. 40, No. 5, pp. 513-524. print.
CODEN: IJEBA6. ISSN: 0019-5189. Language: English.
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AB Cell death is a highly regulated process that is ubiquitous in all
eukaryotes. Programmed cell death (PCD) is an integral part of both
animal and plant development. Studies on apoptosis, the well
characterized form of programmed cell death led to the identification of a
central tripartite death switch i.e. apoptosome consisting of Apaf-1,
Apaf-2 and Apaf-3. The caspases, a family of cysteine-dependent aspartate
directed-proteases, constitute the central executioners of apoptosis.
Much of the attention on programmed cell death is focused on caspases,
however, cell death can still occur even when the caspase cascade is
blocked, revealing the existence of nonapoptotic alternative pathway(s) of
cell death. The mitochondrial release of cytochrome C following a PCD
inducing stimulus in both plants and animals suggests the evolutionary
conservation of death pathways. Dysregulation of apoptosis may be related
to the development of several disease states as well as ageing.
Excessive apoptosis is associated with neurodegenerative
disorders, AIDS etc., whereas deficient apoptosis is associated
with cancer, auto-immunity, viral infections etc. Understanding the
regulation of programmed cell death would throw light in designing drugs
and gene therapies that can target specific molecules in the apoptotic
pathway opening the vistas for new therapeutic endeavors in many areas of
medicine.
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L12 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

2000:628009 Document No. 133:217725 Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof. Shapiro, Leland (The Trustees of University Technology Corporation, USA). PCT Int. Appl. WO 2000051624 A2 20000908, 30 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US6069 20000303. PRIORITY: US 1999-PV123167 19990305.

AB A method is provided for treating an animal suffering a disease characterized by **excessive apoptosis** by administering a therapeutically effective amount of at least one serine protease inhibitor and thereafter monitoring a decrease in apoptosis. The inhibitor of the invention includes α 1-antitrypsin or an α 1-antitrypsin-like agent, including but not limited to oxidation-resistant variants of α 1-antitrypsin, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, autoimmune disease, sepsis neurodegenerative disease, myocardial infarction, stroke, ischemia-reperfusion injury, toxin induced liver injury and **AIDS**. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by **excessive apoptosis**.

=> s l2 and neurodegenerative disease

L13 4 L2 AND NEURODEGENERATIVE DISEASE

=> s l13 and pd<20020602

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L14 2 L13 AND PD<20020602

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PROCESSING COMPLETED FOR L14

L15 2 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-2 cbib abs

L15 ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2002:327025 Document No.: PREV200200327025. Programmed cell death and its clinical implications. Katoch, Bandhana; Sebastian, Sonia; Sahdev, Sudhir; Padh, Harish; Hasnain, Seyed E.; Begum, Rasheedunnisa [Reprint author]. Department of Biochemistry, M. S. University of Baroda, Vadodara, 390 002, India. rasheeda@wilnetonline.net. Indian Journal of Experimental Biology, (May, 2002) Vol. 40, No. 5, pp. 513-524. print. CODEN: IJEBA6. ISSN: 0019-5189. Language: English.

AB Cell death is a highly regulated process that is ubiquitous in all eukaryotes. Programmed cell death (PCD) is an integral part of both animal and plant development. Studies on apoptosis, the well characterized form of programmed cell death led to the identification of a central tripartite death switch i.e. apoptosome consisting of Apaf-1, Apaf-2 and Apaf-3. The caspases, a family of cysteine-dependent aspartate directed-proteases, constitute the central executioners of apoptosis. Much of the attention on programmed cell death is focused on caspases, however, cell death can still occur even when the caspase cascade is blocked, revealing the existence of nonapoptotic alternative pathway(s) of cell death. The mitochondrial release of cytochrome C following a PCD inducing stimulus in both plants and animals suggests the evolutionary conservation of death pathways. Dysregulation of apoptosis may be related to the development of several disease states as well as ageing.

Excessive apoptosis is associated with neurodegenerative disorders, AIDS etc., whereas deficient apoptosis is associated with cancer, auto-immunity, viral infections etc. Understanding the regulation of programmed cell death would throw light in designing drugs and gene therapies that can target specific molecules in the apoptotic pathway opening the vistas for new therapeutic endeavors in many areas of medicine.

L15 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

2000:628009 Document No. 133:217725 Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof. Shapiro, Leland (The Trustees of University Technology Corporation, USA). PCT Int. Appl. WO 2000051624 A2 **20000908**, 30 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US6069 20000303. PRIORITY: US 1999-PV123167 19990305.

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=> s l2 and ischemic injury

L16 1 L2 AND ISCHEMIC INJURY

=> d l6 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN

2004:20982 Document No. 140:90312 A method for the **detection** of apoptosis via determination of nucleolin and/or PARP-1 in the sample. Bates, Paula J.; Mi, Yingchang (University of Louisville Research Foundation, Inc., USA). PCT Int. Appl. WO 2004003554 A1 20040108, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US20167 20030626. PRIORITY: US 2002-392143P 20020626.

AB Methods for the **detection** of apoptosis by measuring apoptotic bodies shed by apoptotic cells are provided, as are kits to carry out such methods. The method comprises preparing a sample from which cells have been removed and determining at least one of nucleolin and PARP-1 in the sample.

The

detection of either (or both) compds. comprises the **detection** of a nucleolin (PARP-1)-binding mol.-nucleolin (PARP-1) complex. The binding mols. are anti-nucleolin (**anti-**

PARP-1) antibodies and for nucleolin also guanosine-rich oligonucleotides. The sample can be blood, serum, plasma, tissue, tissue culture medium, or sputum. The method can be used to determine **excessive apoptosis** via preparing a blood sample from a subject suspected of having a disease selected from the group consisting of AIDS, neurodegenerative disease, ischemic injury, autoimmune disease, tumor, cancer, viral infection, acute inflammation, and sepsis.

=> s l2 and autoimmune disease
L17 7 L2 AND AUTOIMMUNE DISEASE

=> s l17 and pd<20020602
2 FILES SEARCHED...
L18 3 L17 AND PD<20020602

=> dup remove l18
PROCESSING COMPLETED FOR L18
L19 3 DUP REMOVE L18 (0 DUPLICATES REMOVED)

=> d l19 1-3 cbib abs

L19 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2002:327025 Document No.: PREV200200327025. Programmed cell death and its clinical implications. Katoch, Bandhana; Sebastian, Sonia; Sahdev, Sudhir; Padh, Harish; Hasnain, Seyed E.; Begum, Rasheedunnisa [Reprint author]. Department of Biochemistry, M. S. University of Baroda, Vadodara, 390 002, India. rasheeda@wilnetonline.net. Indian Journal of Experimental Biology, (May, 2002) Vol. 40, No. 5, pp. 513-524. print. CODEN: IJEBA6. ISSN: 0019-5189. Language: English.

AB Cell death is a highly regulated process that is ubiquitous in all eukaryotes. Programmed cell death (PCD) is an integral part of both animal and plant development. Studies on apoptosis, the well characterized form of programmed cell death led to the identification of a central tripartite death switch i.e. apoptosome consisting of Apaf-1, Apaf-2 and Apaf-3. The caspases, a family of cysteine-dependent aspartate directed-proteases, constitute the central executioners of apoptosis. Much of the attention on programmed cell death is focused on caspases, however, cell death can still occur even when the caspase cascade is blocked, revealing the existence of nonapoptotic alternative pathway(s) of cell death. The mitochondrial release of cytochrome C following a PCD inducing stimulus in both plants and animals suggests the evolutionary conservation of death pathways. Dysregulation of apoptosis may be related to the development of several disease states as well as ageing. **Excessive apoptosis** is associated with neurodegenerative disorders, AIDS etc., whereas deficient apoptosis is associated with cancer, auto-immunity, viral infections etc. Understanding the regulation of programmed cell death would throw light in designing drugs and gene therapies that can target specific molecules in the apoptotic pathway opening the vistas for new therapeutic endeavors in many areas of medicine.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN 2000:628009 Document No. 133:217725 Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof. Shapiro, Leland (The Trustees of University Technology Corporation, USA). PCT Int. Appl. WO 2000051624 A2 20000908, 30 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US6069 20000303.

PRIORITY: US 1999-PV123167 19990305.

AB A method is provided for treating an animal suffering a disease characterized by **excessive apoptosis** by administering a therapeutically effective amount of at least one serine protease inhibitor and thereafter monitoring a decrease in apoptosis. The inhibitor of the invention includes α 1-antitrypsin or an α 1-antitrypsin-like agent, including but not limited to oxidation-resistant variants of α 1-antitrypsin, and peptoids with antitrypsin activity. The diseases treatable by the invention include cancer, **autoimmune disease**, sepsis neurodegenerative disease, myocardial infarction, stroke, ischemia-reperfusion injury, toxin induced liver injury and AIDS. The method of the invention is also suitable for the prevention or amelioration of diseases characterized by **excessive apoptosis**.

L19 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 1997:462823 Document No.: PREV199799762026. Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of Fas antigen. Hagimoto, Naoki [Reprint author]; Kuwano, Kazuyoshi; Miyazaki, Hiroyuki; Kunitake, Ritsuko; Fujita, Masaki; Kawasaki, Masayuki; Kaneko, Yumi; Hara, Nobuyuki. Fac. Med., Res. Inst. Dis. Chest, Kyushu Univ., 3-1-1 Maidashi, Higashiku, Fukuoka 812, Japan. American Journal of Respiratory Cell and Molecular Biology, (1997) Vol. 17, No. 3, pp. 272-278. CODEN: AJRBEL. ISSN: 1044-1549. Language: English.

AB Fas antigen is a cell surface protein that mediates apoptosis, and it is expressed in various cells and tissues. Fas ligand binds to its receptor Fas, thus inducing apoptosis of Fas-bearing cells. Malfunction of the Fas-Fas ligand system causes lymphoproliferative disorders and **autoimmune diseases**, whereas its exacerbation may cause tissue destruction. We hypothesize that **excessive apoptosis** mediated by Fas-Fas ligand interaction may damage alveolar epithelial cells and result in pulmonary fibrosis. Mice were allowed to inhale repeatedly an aerosolized anti-Fas antibody for 14 days. The nuclei of bronchial and alveolar epithelial cells were positively stained by in situ DNA nick end labeling. Electron microscopy demonstrated apoptotic changes in bronchial and alveolar epithelial cells. Histologic findings and hydroxyproline content showed the development of pulmonary fibrosis, which was dependent on the dose of anti-Fas antibody. The repeated inhalation of control antibody (isotype-matched control hamster IgG) did not induce apoptosis of epithelial cells or pulmonary fibrosis. The expression of TGF-beta mRNA was upregulated from day 7 to day 28 in lung tissues of anti-Fas antibody-treated mice but not in those of control mice. In this report, we present the evidence that repeated inhalation of anti-Fas antibody mimicking Fas-Fas ligand crosslinking induces **excessive apoptosis** and inflammation, which results in pulmonary fibrosis in mice.

=> s 12 and cancer

L20 15 L2 AND CANCER

=> s 120 and pd<20020602

2 FILES SEARCHED...

L21 3 L20 AND PD<20020602

=> d 121 1-3 cbib abs

L21 ANSWER 1 OF 3 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

1999009645 EMBASE 'Low-risk' myelodysplastic syndrome is associated with **excessive apoptosis** and an increased ratio of pro-versus anti-apoptotic bcl-2-related proteins. Parker J.E.; Fishlock K.L.; Mijovic A.; Czepulkowski B.; Pagliuca A.; Mufti G.J.. Prof. G.J. Mufti, Department of Haematology, King's College Hospital, School of Medicine and Dentistry, Bessemer Road, London SE5 9RS, United Kingdom. British Journal

of Haematology Vol. 103, No. 4, pp. 1075-1082 1998.

Refs: 30.

ISSN: 0007-1048. CODEN: BJHEAL

Pub. Country: United Kingdom. Language: English. Summary Language: English.

Entered STN: 19990128. Last Updated on STN: 19990128

- AB We performed flow cytometric analysis of CD34(+) cell apoptosis in 59 patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) secondary to MDS (MDS-AML) using annexin V-FITC, which binds to exposed phosphatidylserine on apoptotic cells. Apoptosis was significantly increased in FAB subtypes RA, RARS and RAEB (<10% blasts) (56.5% (15.1-86.5%)) compared to normal controls (18.5% (3.4-33.4%)), $P < 0.0001$ and RAEB-t/MDS-AML (16% (2.1-43.2%)), $P < 0.0001$. There was no correlation between % apoptosis. Full blood count or cytogenetics in any disease category. Two-colour cytometric analysis of permeabilized CD34(+) cells stained with antibodies to Bcl-2, Bcl-X (anti-apoptotic), Bax and Bad (proapoptotic), demonstrated significantly higher ratios of pro- v anti-apoptotic proteins in early MDS (2.47 (1.19-9.42)) compared to advanced disease (1.14 (0.06-3.32)). $P = 0.0001$. Moreover, using repeated measures of variants (ANOVA), we found that variations between individual Bcl-2-related proteins differed significantly according to disease subtype ($P < 0.0005$). Our results confirm that CD34(+) cell apoptosis was significantly increased in MDS subtypes RA and RARS and fell with disease progression. Early MDS was also associated with a significantly higher CD34(+) cell pro- v anti-apoptotic Bcl-2-family-protein ratio than advanced disease. Furthermore, patterns of expression of individual Bcl-2 related proteins differed significantly between different disease categories. However, no correlation between pro-v anti-apoptotic Bcl-2-family-protein ratios and the degree of apoptosis was observed.

L21 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2002:327025 Document No.: PREV200200327025. Programmed cell death and its clinical implications. Katoch, Bandhana; Sebastian, Sonia; Sahdev, Sudhir; Padh, Harish; Hasnain, Seyed E.; Begum, Rasheedunnisa [Reprint author]. Department of Biochemistry, M. S. University of Baroda, Vadodara, 390 002, India. rasheeda@wilnetonline.net. Indian Journal of Experimental Biology, (May, 2002) Vol. 40, No. 5, pp. 513-524. print. CODEN: IJEBA6. ISSN: 0019-5189. Language: English.

- AB Cell death is a highly regulated process that is ubiquitous in all eukaryotes. Programmed cell death (PCD) is an integral part of both animal and plant development. Studies on apoptosis, the well characterized form of programmed cell death led to the identification of a central tripartite death switch i.e. apoptosome consisting of Apaf-1, Apaf-2 and Apaf-3. The caspases, a family of cysteine-dependent aspartate directed-proteases, constitute the central executioners of apoptosis. Much of the attention on programmed cell death is focused on caspases, however, cell death can still occur even when the caspase cascade is blocked, revealing the existence of nonapoptotic alternative pathway(s) of cell death. The mitochondrial release of cytochrome C following a PCD inducing stimulus in both plants and animals suggests the evolutionary conservation of death pathways. Dysregulation of apoptosis may be related to the development of several disease states as well as ageing. **Excessive apoptosis** is associated with neurodegenerative disorders, AIDS etc., whereas deficient apoptosis is associated with **cancer**, auto-immunity, viral infections etc. Understanding the regulation of programmed cell death would throw light in designing drugs and gene therapies that can target specific molecules in the apoptotic pathway opening the vistas for new therapeutic endeavors in many areas of medicine.

L21 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN 2000:628009 Document No. 133:217725 Methods and compositions using serine protease inhibitors useful in inhibiting apoptosis, and therapeutic use thereof. Shapiro, Leland (The Trustees of University Technology

Corporation, USA). PCT Int. Appl. WO 2000051624 A2 20000908, 30
 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,
 CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
 ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
 MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
 TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU,
 TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR,
 GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG.
 (English). CODEN: PIXXD2. APPLICATION: WO 2000-US6069 20000303.
 PRIORITY: US 1999-PV123167 19990305.

AB A method is provided for treating an animal suffering a disease
 characterized by **excessive apoptosis** by administering
 a therapeutically effective amount of at least one serine protease inhibitor
 and thereafter monitoring a decrease in apoptosis. The inhibitor of the
 invention includes α 1-antitrypsin or an α 1-antitrypsin-like
 agent, including but not limited to oxidation-resistant variants of
 α 1-antitrypsin, and peptoids with antitrypsin activity. The
 diseases treatable by the invention include **cancer**, autoimmune
 disease, sepsis neurodegenerative disease, myocardial infarction, stroke,
 ischemia-reperfusion injury, toxin induced liver injury and AIDS. The
 method of the invention is also suitable for the prevention or
 amelioration of diseases characterized by **excessive**
apoptosis.

=> s l2 and neucleolin
 L22 0 L2 AND NEUCLEOLIN

=> s l22 and PARP
 L23 0 L22 AND PARP

=> d his

(FILE 'HOME' ENTERED AT 14:13:57 ON 30 JAN 2008)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 14:14:12 ON
 30 JAN 2008

L1 753 S EXCESSIVE APOPTOSIS
 L2 163 S L1 AND BLOOD
 L3 10 S L2 AND DETECTION
 L4 6 DUP REMOVE L3 (4 DUPLICATES REMOVED)
 L5 1 S L4 AND ANTI-NUCLEOLIN
 L6 1 S L4 AND ANTI-PARP
 L7 6 DUP REMOVE L3 (4 DUPLICATES REMOVED)
 L8 5 S L7 AND PD<20020602
 L9 0 S L2 AND ACQUIRED IMMUNODEFICIENCY SYNDROME
 L10 3 S L2 AND AIDS
 L11 3 DUP REMOVE L10 (0 DUPLICATES REMOVED)
 L12 2 S L11 AND PD<20020602
 L13 4 S L2 AND NEURODEGENERATIVE DISEASE
 L14 2 S L13 AND PD<20020602
 L15 2 DUP REMOVE L14 (0 DUPLICATES REMOVED)
 L16 1 S L2 AND ISCHEMIC INJURY
 L17 7 S L2 AND AUTOIMMUNE DISEASE
 L18 3 S L17 AND PD<20020602
 L19 3 DUP REMOVE L18 (0 DUPLICATES REMOVED)
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 L21 3 S L20 AND PD<20020602
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 L23 0 S L22 AND PARP

=> s antibod?
 L24 3071424 ANTIBOD?

=> s l24 and nucleolin

L25 731 L24 AND NUCLEOLIN

=> s l25 and anti-nucleolin

L26 134 L25 AND ANTI-NUCLEOLIN

=> s l26 and apoptosis

L27 18 L26 AND APOPTOSIS

=> s l27 and pd<20020602

2 FILES SEARCHED...

L28 6 L27 AND PD<20020602

=> d l28 1-6 cbib abs

L28 ANSWER 1 OF 6 MEDLINE on STN

2002216144. PubMed ID: 11948683. **Nucleolin** is a calcium-binding protein. Gilchrist James S C; Abrenica Bernard; DiMario Patrick J; Czubryt Michael P; Pierce Grant, N. (Department of Oral Biology and Physiology, Division of Stroke and Vascular Disease, University of Manitoba, Winnipeg, Manitoba, Canada.) Journal of cellular biochemistry, (2002) Vol. 85, No. 2, pp. 268-78. Journal code: 8205768. ISSN: 0730-2312. Pub. country: United States. Language: English.

AB We have purified a prominent 110-kDa protein (p110) from 1.6 M NaCl extracts of rat liver nuclei that appears to bind Ca^{2+} . p110 was originally identified by prominent blue staining with 'Stains-All' in sodium dodecyl sulfate-polyacrylamide gels and was observed to specifically bind ruthenium red and $^{45}\text{Ca}^{2+}$ in nitrocellulose blot overlays. In spin-dialysis studies, purified p110 saturably bound approximately 75 nmol Ca^{2+} /mg protein at a concentration of 1 mM total Ca^{2+} with half-maximal binding observed at 105 μM Ca^{2+} . With purification, p110 became increasingly susceptible to proteolytic (likely autolytic) fragmentation, although most intermediary peptides between 40 and 90 kDa retained "Stains-All", ruthenium red, and $^{45}\text{Ca}^{2+}$ binding. N-terminal sequencing of intact p110 and a 70-kDa autolytic peptide fragment revealed a strong homology to **nucleolin**. Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)/IEF revealed autolysis produced increasingly acidic peptide fragments ranging in apparent pI's from 5.5 for intact p110 to 3.5 for a 40 kDa peptide fragment. Intact p110 and several peptide fragments were immunostained with a highly specific **anti-nucleolin antibody**, R2D2, thus confirming the identity of this protein with **nucleolin**. These annexin-like Ca^{2+} -binding characteristics of **nucleolin** are likely contributed by its highly acidic argyrophilic N-terminus with autolysis apparently resulting in largely selective removal of its basic C-terminal domain. Although the Ca^{2+} -dependent functions of **nucleolin** are unknown, we discuss the possibility that like the structurally analogous HMG-1, its Ca^{2+} -dependent actions may regulate chromatin structure, possibly during **apoptosis**. Copyright 2002 Wiley-Liss, Inc.

L28 ANSWER 2 OF 6 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

2002127037 EMBASE **Nucleolin** is a calcium-binding protein. Gilchrist J.S.C.; Abrenica B.; DiMario P.J.; Czubryt M.P.; Pierce G.N.. J.S.C. Gilchrist, Division of Vascular Disease, St. Boniface Gen. Hosp. Res. Centre, 351 Tache Avenue, Winnipeg, Man., R2H 2A6, Canada. Journal of Cellular Biochemistry Vol. 85, No. 2, pp. 268-278 2002. Refs: 72.

ISSN: 0730-2312. CODEN: JCEBD5

Pub. Country: United States. Language: English. Summary Language: English. Entered STN: 20020425. Last Updated on STN: 20020425

AB We have purified a prominent 110-kDa protein (p110) from 1.6 M NaCl extracts of rat liver nuclei that appears to bind Ca^{2+} . p110 was originally identified by prominent blue staining with 'Stains-All' in sodium dodecyl sulfate-polyacrylamide gels and was observed to

specifically bind ruthenium red and (45)Ca(2+) in nitrocellulose blot overlays. In spin-dialysis studies, purified p110 saturably bound approximately 75 nmol Ca(2+)/mg protein at a concentration of 1 mM total Ca(2+) with half-maximal binding observed at 105 μ M Ca(2+). With purification, p110 became increasingly susceptible to proteolytic (likely autolytic) fragmentation, although most intermediary peptides between 40 and 90 kDa retained "Stains-All", ruthenium red, and (45)Ca(2+) binding. N-terminal sequencing of intact p110 and a 70-kDa autolytic peptide fragment revealed a strong homology to **nucleolin**.

Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)/IEF revealed autolysis produced increasingly acidic peptide fragments ranging in apparent pI's from 5.5 for intact p110 to 3.5 for a 40 kDa peptide fragment. Intact p110 and several peptide fragments were immunostained with a highly specific **anti-nucleolin antibody**, R2D2, thus confirming the identity of this protein with **nucleolin**. These annexin-like Ca(2+)-binding characteristics of **nucleolin** are likely contributed by its highly acidic argyrophilic N-terminus with autolysis apparently resulting in largely selective removal of its basic C-terminal domain. Although the Ca(2+)-dependent functions of **nucleolin** are unknown, we discuss the possibility that like the structurally analogous HMG-1, its Ca(2+)-dependent actions may regulate chromatin structure, possibly during **apoptosis**.

.COPYRGT. 2002 Wiley-Liss, Inc.

L28 ANSWER 3 OF 6 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2002:271588 Document No.: PREV200200271588. **Nucleolin** is a calcium-binding protein. Gilchrist, James S. C. [Reprint author]; Abrenica, Bernard; DiMario, Patrick J.; Czubryt, Michael P.; Pierce, Grant N.. Division of Stroke and Vascular Disease, St. Boniface General Hospital Research Centre, 351 Tache Avenue, Room 4024, Winnipeg, Manitoba, R2H 2A6, Canada. Journal of Cellular Biochemistry, (2002) Vol. 85, No. 2, pp. 268-278. print. CODEN: JCEBD5. ISSN: 0730-2312. Language: English.

AB We have purified a prominent 110-kDa protein (p110) from 1.6 M NaCl extracts of rat liver nuclei that appears to bind Ca2+. p110 was originally identified by prominent blue staining with 'Stains-All' in sodium dodecyl sulfate-polyacrylamide gels and was observed to specifically bind ruthenium red and 45Ca2+ in nitrocellulose blot overlays. In spin-dialysis studies, purified p110 saturably bound approximately 75 nmol Ca2+/mg protein at a concentration of 1 mM total Ca2+ with half-maximal binding observed at 105 μ M Ca2+. With purification, p110 became increasingly susceptible to proteolytic (likely autolytic) fragmentation, although most intermediary peptides between 40 and 90 kDa retained "Stains-All", ruthenium red, and 45Ca2+ binding. N-terminal sequencing of intact p110 and a 70-kDa autolytic peptide fragment revealed a strong homology to **nucleolin**. Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)/IEF revealed autolysis produced increasingly acidic peptide fragments ranging in apparent pI's from 5.5 for intact p110 to 3.5 for a 40 kDa peptide fragment. Intact p110 and several peptide fragments were immunostained with a highly specific **anti-nucleolin antibody**, R2D2, thus confirming the identity of this protein with **nucleolin**. These annexin-like Ca2+-binding characteristics of **nucleolin** are likely contributed by its highly acidic argyrophilic N-terminus with autolysis apparently resulting in largely selective removal of its basic C-terminal domain. Although the Ca2+-dependent functions of **nucleolin** are unknown, we discuss the possibility that like the structurally analogous HMG-1, its Ca2+-dependent actions may regulate chromatin structure, possibly during **apoptosis**.

L28 ANSWER 4 OF 6 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN

2002:318586 The Genuine Article (R) Number: 538JX. **Nucleolin** is a calcium-binding protein. Gilchrist J S C (Reprint); Abrenica B; Dimario P J; Czubryt M P; Pierce G N. St Boniface Gen Hosp, Div Stroke & Vasc Dis,

Rm 4024 351 Tache Ave, Winnipeg, MB R2H 2A6, Canada (Reprint); Univ Manitoba, Div Stroke & Vasc Dis, Dept Oral Biol & Physiol, Winnipeg, MB, Canada; Louisiana State Univ, Dept Sci Biol, Baton Rouge, LA USA; Univ Manitoba, Div Stroke & Vasc Dis, Dept Physiol, Winnipeg, MB, Canada. JOURNAL OF CELLULAR BIOCHEMISTRY (2002) Vol. 85, No. 2, pp. 268-278. ISSN: 0730-2312. Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB

We have purified a prominent 110-kDa protein (p110) from 1.6 M NaCl extracts of rat liver nuclei that appears to bind Ca^{2+} . p-110 was originally identified by prominent blue staining with 'Stains-All' in sodium dodecyl sulfate-polyacrylamide gels and was observed to specifically bind ruthenium red and $\text{Ca-45}(2+)$ in nitrocellulose blot overlays. In spin-dialysis studies, purified p110 saturably bound approximately 75 nmol Ca^{2+}/Mg protein at a concentration of 1 mM total Ca^{2+} with half-maximal binding observed at 105 μM Ca^{2+} . With purification, p110 became increasingly susceptible to proteolytic (likely autolytic) fragmentation, although most intermediary peptides between 40 and 90 kDa retained "Stains-All", ruthenium red, and $\text{Ca-45}(2+)$ binding. N-terminal sequencing of intact p110 and a 70-kDa autolytic peptide fragment revealed a strong homology to **nucleolin**. Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)/IEF revealed autolysis produced increasingly acidic peptide fragments ranging in apparent pI's from 5.5 for intact p110 to 3.5 for a 40 kDa peptide fragment. Intact p110 and several peptide fragments were immunostained with a highly specific **anti-nucleolin antibody**, R2D2, thus confirming the identity of this protein with **nucleolin**. These annexin-like Ca^{2+} -binding characteristics of **nucleolin** are likely contributed by its highly acidic argyrophilic N-terminus with autolysis apparently resulting in largely selective removal of its basic C-terminal domain. Although the Ca^{2+} -dependent functions of **nucleolin** are unknown, we discuss the possibility that like the structurally analogous HMG-1, its Ca^{2+} -dependent actions may regulate chromatin structure, possibly during **apoptosis**. J. Cell. Biochem. 85: 268-278, 2002. (C) 2002 Wiley-Liss, Inc.

L28 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

2002:288903 Document No. 136:397617 **Nucleolin** is a calcium-binding protein. Gilchrist, James S. C.; Abrenica, Bernard; DiMario, Patrick J.; Czubryt, Michael P.; Pierce, Grant N. (Department of Oral Biology and Physiology, Division of Stroke and Vascular Disease, University of Manitoba, Winnipeg, MB, Can.). Journal of Cellular Biochemistry, 85(2), 268-278 (English) 2002. CODEN: JCEBD5. ISSN: 0730-2312. Publisher: Wiley-Liss, Inc..

AB

We have purified a prominent 110-kDa protein (p110) from 1.6 M NaCl exts. of rat liver nuclei that appears to bind Ca^{2+} . P110 was originally identified by prominent blue staining with "Stains-All" in SDS-polyacrylamide gels and was observed to specifically bind ruthenium red and 45Ca^{2+} in nitrocellulose blot overlays. In spin-dialysis studies, purified p110 saturably bound approx. 75 nmol Ca^{2+}/mg protein at a concentration

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removal of its basic C-terminal domain. Although the Ca²⁺-dependent functions of **nucleolin** are unknown, we discuss the possibility that like the structurally analogous HMG-1, its Ca²⁺-dependent actions may regulate chromatin structure, possibly during **apoptosis**.

L28 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2008 ACS on STN

2001:161702 Document No. 134:205322 Protein phosphatases and **apoptosis**: nuclear protein associates with protein phosphatase type 18 isoform. Haneji, Tatsuji (Second Dep. Oral Anat., Sch. Dent., The Univ. Tokushima, Tokushima, 770-8504, Japan). Shikoku Shigakkai Zasshi, 13(2), 221-229 (Japanese) 2001. CODEN: SSZAED. ISSN: 0914-6091. Publisher: Shikoku Shigakkai.

AB A review with 63 refs. Several lines of evidence indicate that protein phosphorylation and dephosphorylation have been recognized as a key mechanism in cell proliferation, differentiation, and **apoptosis** in various tissues. Okadaic acid is a toxic polyether fatty acid produced by dinoflagellates and is a potent inhibitor of protein phosphatase type 1 (PP1) and type 2A (PP2A) that dephosphorylate serine and threonine residues in eukaryotic cells. CDNA cloning revealed the existence of four isoforms of PP1 catalytic subunit in rat, termed PP1 α , PP1 γ 1, PP1 γ 2, and PP1 δ . PP1 targeting subunits is thought to localize to specific subcellular component and to modulate the activity of the enzyme at these sites. **Nucleolin** is an abundantly expressed nucleolar phosphoprotein and is located mainly in nucleolus. Staining pattern of **nucleolin** in MG63 cells is similar to that of the PP1 δ . The dual fluorescence image revealed that PP1 δ and **nucleolin** represent same localization in nucleolus. The **anti-nucleolin antibody** interacted with the 100 kDa protein immunoprecipitated with PP1 δ **antibody**. However, **anti-nucleolin antibody** did not interact with the samples precipitated with the normal rabbit serum. The 100 kDa protein was dephosphorylated into 98 kDa protein by lambda phosphatase. In the actinomycin D-treated cells, subcellular localization of PP1 δ and **nucleolin** was changed. The amount of PP1 δ increased whereas the level of dephosphorylated form of **nucleolin** increased. These results indicate that PP1 δ associate with **nucleolin** directly to dephosphorylate this protein and is involved in r-RNA synthesis. In the present review, I also demonstrate the relationship between protein phosphatases and apoptotic processes in cells including Saos-2, MG63, MC3T3-E1, SCC-25, SCCKN, SCCTF and HSG cells studied in our laboratory

=> s 124 and PARP-1

L29 199 L24 AND PARP-1

=> s 129 and apoptosis

L30 88 L29 AND APOPTOSIS

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L31 21 L30 AND PD<20020602

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L32 8 DUP REMOVE L31 (13 DUPLICATES REMOVED)

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L32 ANSWER 1 OF 8 MEDLINE on STN

DUPLICATE 1

2002122378. PubMed ID: 11857494. **Apoptosis** in B-cell lymphomas and reactive lymphoid tissues always involves activation of caspase 3 as determined by a new in situ detection method. Dukers Danny F; Oudejans Joost J; Vos Wim; ten Berge Rosita L; Meijer Chris J L M. (Department of Pathology, VU Medical Centre Amsterdam, De Boelelaan 1117, 1081 HV

Amsterdam, The Netherlands.) The Journal of pathology, (2002 Mar)
Vol. 196, No. 3, pp. 307-15. Journal code: 0204634. ISSN: 0022-3417. Pub.
country: England: United Kingdom. Language: English.

AB In vitro studies indicate that in lymphomas, execution of
apoptosis involves activation of effector caspases. To
investigate activation of effector caspases in vivo in biopsy specimens of
lymphomas, a new assay was developed using **antibodies** against
active caspase 3 and p89, a protein fragment generated by caspase-specific
cleavage of poly-ADP ribose polymerase (PARP). Using this assay, it was
found that in B-cell lymphomas, levels of active caspase 3/p89-positive
cells correlate strongly with morphologically recognizable apoptotic
cells. The number of active caspase 3/p89-positive cells was low in
follicular lymphomas and usually high in diffuse large cell lymphomas.
Highest numbers were found in Burkitt lymphomas and in two biopsies of
diffuse large B-cell lymphomas (DLCLs) obtained several days after
initiation of therapy. It is concluded that **apoptosis** in
reactive lymphoid tissues and in B-cell lymphomas always involves
activation of effector caspase 3 and cleavage of one of the major effector
caspase substrates, **PARP-1**. Moreover, levels of
effector caspase activation are constantly low in low-grade follicular
lymphomas and vary considerably in DLCL and Burkitt lymphoma.
Copyright 2002 John Wiley & Sons, Ltd.

L32 ANSWER 2 OF 8 MEDLINE on STN DUPLICATE 2
2002370493. PubMed ID: 12114629. Mediation of poly(ADP-ribose)
polymerase-1-dependent cell death by **apoptosis**-inducing factor.
Yu Seong-Woon; Wang Hongmin; Poitras Marc F; Coombs Carmen; Bowers William
J; Federoff Howard J; Poirier Guy G; Dawson Ted M; Dawson Valina L.
(Department of Neurology and Institute for Cell Engineering, Johns Hopkins
University School of Medicine, Baltimore, MD 21287, USA.) Science (New
York, N.Y.), (2002 Jul 12) Vol. 297, No. 5579, pp. 259-63.
Journal code: 0404511. E-ISSN: 1095-9203. Pub. country: United States.
Language: English.

AB Poly(ADP-ribose) polymerase-1 (**PARP-1**) protects the
genome by functioning in the DNA damage surveillance network.
PARP-1 is also a mediator of cell death after
ischemia-reperfusion injury, glutamate excitotoxicity, and various
inflammatory processes. We show that **PARP-1**
activation is required for translocation of **apoptosis**-inducing
factor (AIF) from the mitochondria to the nucleus and that AIF is
necessary for **PARP-1**-dependent cell death.
N-methyl-N'-nitro-N-nitrosoguanidine, H₂O₂, and N-methyl-d-aspartate
induce AIF translocation and cell death, which is prevented by PARP
inhibitors or genetic knockout of **PARP-1**, but is
caspase independent. Microinjection of an **antibody** to AIF
protects against **PARP-1**-dependent cytotoxicity. These
data support a model in which **PARP-1** activation
signals AIF release from mitochondria, resulting in a caspase-independent
pathway of programmed cell death.

L32 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
2003:303624 Document No.: PREV200300303624. NOVEL ISOQUINOLINONE - DERIVED
INHIBITORS OF POLY (ADP - RIBOSE) POLYMERASE - 1 (**PARP** -
1) : PHARMACOLOGICAL CHARACTERIZATION AND NEUROPROTECTIVE EFFECTS
IN MODELS OF CEREBRAL ISCHEMIA. Moroni, F. [Reprint Author]; Chiarugi, A.
[Reprint Author]; Meli, E. [Reprint Author]; Cozzi, A. [Reprint Author];
Baronti, R. [Reprint Author]; Pangallo, M. [Reprint Author]; Camaioni, E.;
Costantino, G.; Marinozzi, M.; Pellicciari, R.; Pellegrini-Giampietro, D.
E. [Reprint Author]. Department of Pharmacology, University of Florence,
Firenze, Italy. Society for Neuroscience Abstract Viewer and Itinerary
Planner, (2002) Vol. 2002, pp. Abstract No. 202.1.
<http://sfn.scholarone.com.cd-rom>.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience.
Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
Language: English.

AB Overactivation of the nuclear enzyme **PARP-1** in response to DNA damage induces a depletion of NAD and ATP cellular stores leading to energy failure and cell death. We have previously shown that **PARP** inhibitors attenuate postischemic neuronal death when necrosis prevails over **apoptosis** (Cell Death Differ. 8: 921, 2001). In this study, we used an in vitro assay to characterize a series of isoquinolinone derivatives: the compound thieno(2,3-c)isoquinolinon-5-one (TIQ) inhibited **PARP-1** activity with an IC50 of 0.1 μ M, being ten time more potent than the reference compound DPQ. We then compared the effects of TIQ and DPQ in cultured cortical cells exposed to oxygen and glucose deprivation (OGD). Both TIQ and DPQ dose-dependently attenuated neuronal injury but at 0.1 and 1 μ M the neuroprotective effect of TIQ was more pronounced than that of DPQ. Flow-cytofluorimetry using a poly(ADP-ribose) (PAR) **antibody** revealed the TIQ was able to reduce the early formation of PAR induced by OGD. In a transient rat model of focal ischemia, the administration of TIQ (3 and 10 mg/Kg, i.p.) and DPQ (10 mg/Kg, i.p.) at 0 and 120 min after the occlusion reduced the infarct volume by 40%, 70% and 48%, respectively. TIQ but not DPQ reduced the infarct volume by 35% when observed 24 h after ischemia. Our results show that TIQ is a novel and potent **PARP-1** inhibitor displaying neuroprotective activity in in vitro and in vivo models of cerebral ischemia.

L32 ANSWER 4 OF 8 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2003:282837 Document No.: PREV200300282837. **APOPTOSIS** - INDUCING FACTOR (AIF) MEDIATES POLY (ADP - RIBOSE) POLYMERASE - 1 DEPENDENT NMDA EXCITOTOXICITY. Wang, H. [Reprint Author]; Yu, S. [Reprint Author]; Poitras, M. F. [Reprint Author]; Kiluk, J. [Reprint Author]; Lew, J. [Reprint Author]; Bowers, W. [Reprint Author]; Federoff, H. J. [Reprint Author]; Poirier, G. G. [Reprint Author]; Dawson, T. M. [Reprint Author]; Dawson, V. L. [Reprint Author]. Dept of Neurology, Johns Hopkins Univ, Baltimore, MD, USA. Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 199.4. <http://sfn.scholarone.com.cd-rom>. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience. Language: English.

AB **Apoptosis**-inducing factor (AIF) is a mitochondrial intermembrane protein that can trigger caspase-independent cell death. Using cultured E15 mouse cortical neurons we have investigated the role of AIF in NMDA-induced excitotoxicity. Administration of 500 μ M NMDA for 5 min elicits neurotoxicity in wild type but not in **PARP-1** KO neurons. Under the same condition, caspase inhibitors (BAF and z-VAD.fmk) fail to block NMD excitotoxicity. After NMDA administration, translocation of AIF to the nucleus precedes cytochrome-c release and caspase-3 activation and is followed by nuclear condensation. These events were not observed in the cultures treated with AMPA, a non-NMDA agonist triggering **PARP-1** independent cytotoxicity. NMDA exposure causes severe DNA fragmentation and **PARP-1** activation in wild type neurons, which appears to be initiated by nitric oxide as the Comet Assay cannot detect damaged DNA fragments in the neurons derived from nNOS KO mice. NMDA exposure triggers decrements of ATP and NAD levels in the wild type neurons, but not in **PARP-1** KO and nNOS KO neurons. Although administration of oligomycin can deplete ATP and NAD to a minimal level, it fails to induce AIF release. Overexpression of Bcl-2 inhibits AIF release and nuclear condensation after NMDA insults. In addition, neutralizing anti-AIF **antibody** significantly reduces NMDA excitotoxicity. These results taken together suggest that AIF mediates NMDA excitotoxicity in a **PARP-1** dependent fashion.

L32 ANSWER 5 OF 8 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN 2001:670570 The Genuine Article (R) Number: 463RQ. Ionising radiation induces the expression of **PARP-1** and **PARP-2** genes in

Arabidopsis. Doucet-Chabeaud G; Godon C; Brutesco C; de Murcia G; Kazmaier M (Reprint). CEA Cadarache, DSV, DEVM, Lab Radiobiol Vegetale, F-13108 St Paul Les Durance, France (Reprint); Ecole Super Biotechnol Strasbourg, CNRS, UPR 9003, CEA, F-67400 Illkirch Graffenstaden, France. MOLECULAR GENETICS AND GENOMICS (AUG 2001) Vol. 265, No. 6, pp. 954-963. ISSN: 1617-4615. Publisher: SPRINGER-VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By screening for Arabidopsis genes activated by ionising radiation (IR)-induced DNA damage, we have isolated a cDNA hybridising with a 3.2-kb mRNA that accumulates rapidly and strongly in irradiated cell suspensions or whole plants. The cDNA codes for a 110-kDa protein that is highly homologous to the 116-kDa vertebrate poly(ADP-ribose) polymerase (PARP-1). It is recognised by a human anti-PARP-1 antibody, binds efficiently to DNA strand interruptions in vitro, and catalyses DNA damage-dependent (ADP-ribose) polymer synthesis. We have named this protein AtPARP-1. We have also extended our observations to the Arabidopsis app (AtPARP-2) gene, demonstrating for the first time that IR-induced DNA strand interruptions induce rapid and massive accumulation of AtPARP-1 and AtPARP-2 transcripts, whereas dehydration and cadmium preferentially induce the accumulation of AtPARP-2 transcripts. The IR-induced PARP gene expression seen in Arabidopsis is in striking contrast to the post-translational activation of the PARP-1 protein that is associated with genotoxic stress in animal cells. AtPARP-1 transcripts accumulate in all plant organs after exposure to ionising radiation, but this is followed by an increase in AtPARP-1 protein levels only in tissues that contain large amounts of actively dividing cells. This cell-type specific accumulation of AtPARP-1 protein in response to DNA damage is compatible with a role for the AtPARP-1 protein in the maintenance of DNA integrity during replication, similar to the role of "guardian of the genome" attributed to its animal counterpart.

L32 ANSWER 6 OF 8 MEDLINE on STN DUPLICATE 3
 2002061641. PubMed ID: 11788790. Disruption of poly (ADP-ribose) polymerase (PARP) protects against stress-evoked immunocompromise. Drazen D L; Bilu D; Edwards N; Nelson R J. (Department of Psychology, The Johns Hopkins University, Baltimore, MD, USA.) Molecular medicine (Cambridge, Mass.), (2001 Nov) Vol. 7, No. 11, pp. 761-6. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Chronic stress, mediated by adrenal hormones, is a major risk factor in the progression and outcome of human disease. While the secretion of adrenal hormones is known to be the primary endocrine mediator of stress-induced immunocompromise, the molecular mechanisms underlying the immunocompromise remain unspecified. Overproduction of the nuclear enzyme, poly (ADP-ribose) polymerase (PARP) has been implicated in the molecular pathway that leads to cell death by energy depletion following stress. MATERIALS AND METHODS: Wild-type (WT) mice and mice with targeted disruption of the gene encoding PARP-1 (PARP-1 -/-) were subjected to 2 wk daily cold-water swim; splenocyte proliferation, anti-KLH IgG, and serum corticosterone concentrations were assessed. Additional mice of each genotype received daily i.p. injections of dexamethasone (DEX) (0.75 mg/kg) for 2 wk, and splenocyte proliferation and anti-KLH IgG were assessed. RESULTS: Splenocyte proliferation and specific antibody concentrations of stressed WT mice were reduced by 20% of their pre-stress levels. In contrast, PARP-1 -/- mice maintained normal cell-mediated and humoral immune function following enforced cold-water swim stress. PARP-1 -/- mice also failed to compromise immune function following DEX treatment, whereas WT mice displayed significant reductions of immune function following this treatment. CONCLUSIONS: These results provide support for the involvement of PARP activation in immunological damage following physical stress. These results suggest that glucocorticoid-induced immunosuppression may require the activation of PARP in order for apoptosis of immune

cells to take place. Taken together, these results suggest that therapies designed to inhibit PARP may prove valuable in the treatment of stress-related diseases.

L32 ANSWER 7 OF 8 MEDLINE on STN DUPLICATE 4
2001226078. PubMed ID: 11171371. Segregation of nucleolar components coincides with caspase-3 activation in cisplatin-treated HeLa cells. Horky M; Wurzer G; Kotala V; Anton M; Vojtesek B; Vacha J; Wesierska-Gadek J. (Department of Pathological Physiology, Faculty of Medicine, Masaryk University, Komenskeho namesti 2, 662 43 Brno, Czech Republic.. mhorky@med.muni.cz) . Journal of cell science, (2001 Feb) Vol. 114, No. Pt 4, pp. 663-70. Journal code: 0052457. ISSN: 0021-9533. Pub. country: England: United Kingdom. Language: English.

AB We studied morphological changes of the nucleoli in HeLa cells treated with cisplatin and compared them with induction of markers of programmed cell death and TUNEL staining. We used different light microscopic nucleolar staining methods allowing us to visualize not only nucleolar proteins but also nucleolar RNA. Our results show predominantly compact, centrally localized nucleoli in intact control HeLa cells. In cisplatin-treated HeLa cells, we found an early onset of nucleolar segregation of proteins detected by argyrophilic nucleolar organizer regions and anti-nucleolar monoclonal **antibody** as well as an increased immunoreactivity for activated caspase-3 after 6 hours. Staining with Toluidine Blue and Methyl-green Pyronine revealed segregated nucleoli 12 hours after the treatment with cisplatin. TUNEL positivity in cisplatin-treated HeLa cells was accompanied by the aggregation of the argyrophilic proteins in the central portion of nucleus, disappearance of nucleolar RNA and shrinkage of the nucleus after 24 hours. Monitoring of the biochemical changes by immunoblotting revealed that activation of distinct caspases and degradation of their downstream protein substrates is executed in two phases. During an early apoptotic stage beginning 4.5 hours post treatment an activation of caspase-9 and caspase-3 was observed. This was accompanied by proteolytic cleavage of poly(ADP-ribose) polymerase-1 (**PARP-1**). The caspase-9 activation seems to be mediated by recruitment by the activating factor Apaf-1 because the increased accumulation of Apaf-1 and cytochrome C in cytosol preceded the generation of mature caspase-9 form. A second phase of **apoptosis** occurring between 10 and 15 hours post treatment was characterized by degradation of other nucleolar and nuclear proteins such as nuclear lamins, topoisomerase I and B23. In conclusion, remarkable segregation of nucleolar argyrophilic proteins, nucleolar RNA and a simultaneous activation of the cascade of caspases markedly preceded the TUNEL positivity in cisplatin-treated HeLa cells thereby substantiating the hypothesis that the nucleolus is a preferred target for caspase-3-dependent proteolysis in cisplatin-treated HeLa cells.

L32 ANSWER 8 OF 8 SCISEARCH COPYRIGHT (c) 2008 The Thomson Corporation on STN
2000:402264 The Genuine Article (R) Number: 315TD. Characterization of sPARP-1 - An alternative product of **PARP-1** gene with poly(ADP-ribose) polymerase activity independent of DNA strand breaks. Sallmann F R; Vodenicharov M D; Wang Z Q; Poirier G G (Reprint). Univ Laval, CHUQ, CHUL Res Ctr, Med Res Ctr, Hlth & Environm Unit, PolyADP Ribose M, 2705 Boul Laurier, St Foy, PQ G1V 4G2, Canada (Reprint); Univ Laval, CHUQ, CHUL Res Ctr, Med Res Ctr, Hlth & Environm Unit, PolyADP Ribose M, St Foy, PQ G1V 4G2, Canada; Univ Laval, Fac Med, St Foy, PQ G1V 4G2, Canada; Int Agcy Res Canc, F-69372 Lyon, France. JOURNAL OF BIOLOGICAL CHEMISTRY (19 MAY 2000) Vol. 275, No. 20, pp. 15504-15511. ISSN: 0021-9258. Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3996 USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Poly(ADP-ribose) polymerase-1 (**PARP-1**) is an abundant nuclear enzyme that catalyzes the synthesis of poly(ADP-ribose) (pADPr) from its substrate NAD(+) upon binding to DNA strand breaks.

Poly(ADP-ribosyl)ation has been implicated in many cellular processes including replication, transcription, and the maintenance of genomic stability. However, studies with mice and cells lacking **PARP-1** reveal a critical role for the enzyme in the maintenance of genomic integrity only. Recently, a significant level of poly(ADP-ribose) polymerase activity has been detected in fibroblasts derived from mice lacking **PARP-1** following treatment with genotoxic agents (Shieh, W. M., AmB, J-C., Wilson, M. V., Wang, Z-Q., Koh, D. W., Jacobson, M. K., and Jacobson, E. L. (1998) J. Biol. Chemical 273, 30069-30072). We have isolated a cDNA that originates from **PARP-1** (-/-) fibroblasts and encodes a polypeptide of 493 amino acid residues bearing poly(ADP-ribose) polymerase activity. This protein, that we named **sPARP-1** for short poly(ADP-ribose) polymerase-1, has a calculated mass of 55.3 kDa and is identical in deduced amino acid sequence to the catalytic domain of **PARP-1**. Radiation hybrid analysis assigned the **sPARP-1** gene to the chromosome 1H5-H6 in an immediate proximity to the known location of **PARP-1** gene, indicating that **sPARP-1** and **PARP-1** are most probably products of the same gene. Active **sPARP-1** is present in both **PARP-1** (+/+) and **PARP-1** (-/-) cells as demonstrated by activity-Western blotting and immunostaining using a specific antibody developed against **sPARP-1**. Like **PARP-1**, **sPARP-1** is localized in the cell nucleus, uses NAD(+) as a substrate and is inhibited by nicotinamide analogues. **sPARP-1** produces PADPr of similar length and structure to that of **PARP-1**. However, contrary to **PARP-1**, **sPARP-1** does not require DNA strand breaks for its activation, although it is stimulated following genotoxic treatments.

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L33      3444 (BATES P?/AU OR MI Y?/AU)
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=> s l33 and apoptosis
L34      47 L33 AND APOPTOSIS
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=> s l34 and blood
L35      5 L34 AND BLOOD
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L36      5 DUP REMOVE L35 (0 DUPLICATES REMOVED)
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nested terms that are not separated by a logical operator.
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L36 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2008 ACS on STN
2004:20982 Document No. 140:90312 A method for the detection of
apoptosis via determination of nucleolin and/or PARP-1 in the
sample. Bates, Paula J.; Mi, Yingchang (University of
Louisville Research Foundation, Inc., USA). PCT Int. Appl. WO 2004003554
A1 20040108, 66 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,
KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,
GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.
(English). CODEN: PIXXD2. APPLICATION: WO 2003-US20167 20030626.
PRIORITY: US 2002-392143P 20020626.
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AB Methods for the detection of **apoptosis** by measuring apoptotic bodies shed by apoptotic cells are provided, as are kits to carry out such methods. The method comprises preparing a sample from which cells have been removed and determining at least one of nucleolin and PARP-1 in the sample.

The

detection of either (or both) compds. comprises the detection of a nucleolin (PARP-1)-binding mol.-nucleolin (PARP-1) complex. The binding mols. are anti-nucleolin (anti-PARP-1) antibodies and for nucleolin also guanosine-rich oligonucleotides. The sample can be **blood**, serum, plasma, tissue, tissue culture medium, or sputum. The method can be used to determine excessive **apoptosis** via preparing a **blood** sample from a subject suspected of having a disease selected from the group consisting of AIDS, neurodegenerative disease, ischemic injury, autoimmune disease, tumor, cancer, viral infection, acute inflammation, and sepsis.

L36 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2005:3439 Document No.: PREV200500007141. Effects of follicle-stimulating hormone and androgen on proliferation of cultured testicular germ cells of embryonic chickens. **Mi, Yuling**; Zhang, Calqiao [Reprint Author]; Xie, Meina; Zeng, Weidong. Coll Anim SciDept Vet Med, Zhejiang Univ, Hangzhou, 310029, China. cqzhang@zju.edu.cn. General and Comparative Endocrinology, (September 15 2004) Vol. 138, No. 3, pp. 237-246. print. CODEN: GCENA5. ISSN: 0016-6480. Language: English.

AB A germ-Sertoli cell coculture model was established to study effects of follicle-stimulating hormone (FSH) and testosterone (T) on testicular germ cell proliferation of the embryonic chickens. Germ and somatic cells were dispersed from 18-day-old embryonic testes and cultured in 96-well plates. Germ cells were characterized by expression of stem cell factor receptor c-kit. Germ cell proliferation was assessed by an increase in cell number and expression of proliferating cell nuclear antigen (PCNA). Results showed that the germ and Sertoli cells kept alive in serum-free McCoy's 5A medium supplemented with insulin, transferrin, and selenite (ITS medium). Germ cells adhered to the free surface of Sertoli cells that spread the filopodia and formed a monolayer in ITS medium. In the serum-containing medium, Sertoli cells displayed an increment with a flat squamous form and only a few very large germ cell masses were found in the free surface of Sertoli cells. Many germ cells showed **apoptosis** in the McCoy's 5A medium without ITS or serum. Only germ cells showed positive staining for c-kit in the coculture. Ovine FSH (0.25-1.01 U/ml) significantly increased the number of germ cells, and PCNA-labeling index ($P < 0.05$). FSH also induced stronger c-kit expression compared with the control. In the FSH-treated groups, germ cells were manifested distinct knob-like form. Similar stimulating effect was found in the germ cell number by T treatments (10^{-7} - 10^{-6} M). Furthermore, FSH (0.51 U/ml) combined with T significantly promoted higher testicular germ cell proliferation ($P < 0.05$) compared with either FSH or T alone, which indicated that interaction of FSH and T might be additive. The above results showed that the serum-free germ-Sertoli cell coculture model allowed evaluating hormonal regulation of testicular germ cell proliferation. FSH and T promoted testicular germ cell proliferation probably through indirect effects on Sertoli cells. Copyright 2004 Published by Elsevier Inc.

L36 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2003:201624 Document No.: PREV200300201624. **Apoptosis** in leukemia cells is accompanied by alterations in the levels and localization of nucleolin. **Mi, Yingchang**; Thomas, Shelia D.; Xu, Xiaohua; Casson, Lavona K.; Miller, Donald M.; **Bates, Paula J.** [Reprint Author]. 570 S. Preston St., 204B Baxter Bldg., Louisville, KY, 40202, USA. paula.bates@louisville.edu. Journal of Biological Chemistry, (March 7 2003) Vol. 278, No. 10, pp. 8572-8579. print. CODEN: JBCHA3. ISSN: 0021-9258. Language: English.

AB Molecular defects in apoptotic pathways are thought to often contribute to the abnormal expansion of malignant cells and their resistance to chemotherapy. Therefore, a comprehensive knowledge of the mechanisms

controlling induction of **apoptosis** and subsequent cellular disintegration could result in improved methods for prognosis and treatment of cancer. In this study, we have examined **apoptosis**-induced alterations in two proteins, nucleolin and poly(ADP-ribose) polymerase-1 (PARP-1), in U937 leukemia cells. Nucleolin is expressed at high levels in malignant cells, and it is a multifunctional and mobile protein that can shuttle among the nucleolus, nucleoplasm, cytoplasm, and plasma membrane. Here, we report our findings that UV irradiation or camptothecin treatment of U937 cells induced **apoptosis** and caused a significant change in the levels and localization of nucleolin within the nucleus. Additionally, nucleolin levels were dramatically decreased in extracts containing the cytoplasm and plasma membrane. These alterations could be abrogated by pre-incubation with an inhibitor of PARP-1 (3-aminobenzamide), and our data support a potential role for nucleolin in removing cleaved PARP-1 from dying cells. Furthermore, both nucleolin and cleaved PARP-1 were detected in the culture medium of cells undergoing **apoptosis**, associated with particles of a size consistent with apoptotic bodies. These results indicate that nucleolin plays an important role in **apoptosis**, and could be a useful marker for assessing **apoptosis** or detecting apoptotic bodies. In addition, the data provide a possible explanation for the appearance of nucleolin and PARP-1 autoantibodies in some autoimmune diseases.

L36 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2002:151933 Document No.: PREV200200151933. Regulation of nucleolin in U937 cells treated with UV-light and cytotoxic drugs. **Mi, Yingchang** [Reprint author]; Rates, Paula J. [Reprint author]; Thomas, Shelia D. [Reprint author]; Xu, Xiaohua [Reprint author]; Casson, Lavona [Reprint author]; Miller, Donald M. [Reprint author]. James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA. Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 139b. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2. Orlando, Florida, USA. December 07-11, 2001. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB Levels of the nucleolar protein, nucleolin, are positively correlated with cell proliferation rate, and therefore elevated in cancer cells compared to normal cells. Nucleolin is a multifunctional protein that has been implicated in many processes, including ribosome biogenesis, DNA replication, cell cycle progression and **apoptosis**. It has been identified as an **apoptosis**-associated protein in human Burkitt lymphoma cell line, and is cleaved by caspase-3. Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in DNA repair and one of intracellular "death substrates", can also be cleaved by caspase-3. In this study, U937 (monocytic leukemia) cells were irradiated with UV-light or treated with 20 mM cytosine arabinoside (Ara-C), 10 mM camptothecin (CPT) for different times (2, 4, 8, 24 h) in the absence or presence of 3-aminobenzamide (3-ABA), an inhibitor of PARP. Alterations of nucleolin in both cytoplasm and nucleus, and PARP in nucleus were investigated by western blot analysis. Cell cycle parameters were determined using flow cytometry with PI staining. Nucleolin in the cytoplasm decreased 4h after UV-irradiation and did not come back until 72h. Nucleolin in the nucleus decreased 2h after UV-irradiation, and recovered 48h later. The active form of PARP (118-KD protein) began cleavage to an inactive form (89 Kda) 2h after UV-irradiation, became undetectable at 4h, and came back at 48h. 3-ABA pre-incubation could inhibit PARP cleavage by more than 50% at 4h, 8h, 24h. At the same time, 3-ABA also reduced the disappearance of nucleolin (both in cytoplasm and nucleus). We also compared cell cycle after UV-irradiation between 3-ABA pre-incubated and no 3-ABA treatment groups. Percentage of sub-G1 phase cells was the highest at 4h, and decreased gradually. The 3-ABA pre-incubated group had a higher percentage of S phase cells and a lower ratio of sub-G1 phase cells. Furthermore, we treated U937 cells using Ara-C and CPT, and found that nucleolin both in cytoplasm and nucleus was down-regulated over time and decreased markedly by 8h. PARP was cleaved to its inactive form at 4h.

Although pre-incubation with 3-ABA before drug treatment did not protect PARP cleavage, it protected nucleolin from decreasing (although to a lesser extent than in UV-irradiated cells). Using immunoprecipitation/western blot we determined that nucleolin and PARP could form a complex. Conclusions: Nucleolin plays an important role in leukemia cell **apoptosis**/death induced by anti-neoplastic agents and UV-irradiation. Alteration of nucleolin in nucleus precludes that in the cytoplasm. Nucleolin can form a complex with PARP, and acts as one of the substrates of PARP. Nucleolin is therefore a component of the caspase-dependent cell **apoptosis** mechanism.

L36 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN 2001:301451 Document No.: PREV200100301451. Guanosine-rich oligonucleotides inhibit proliferation of leukemia cells. Castillos, Francisco A., III [Reprint author]; Bates, Paula J. [Reprint author]; Thomas, Shelia D. [Reprint author]; Xu, Xiaohua [Reprint author]; Trent, John O. [Reprint author]; Miller, Donald M. [Reprint author]. Hematology/Medical Oncology James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 308a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB We have tested the ability of a G-quartet forming Guanosine-rich oligonucleotide GRO29A to inhibit growth of several leukemia cell-lines in vitro. GRO29A is a novel oligonucleotide which has its effects by non-antisense mechanisms. MTT assays were performed to determine dose-response to GRO29A in U937, K562, HL-60, MEG01, and RS4:11 leukemia cell-lines and the mouse hematopoietic progenitor stem-cell line ATCC 2037. We demonstrated IC50s ranging from 2.0 to 2.5 μ M for leukemia cell-lines with differential survival of a population of mouse hematopoietic progenitor cells in the 10 μ M range. Time course assays demonstrate a sustained inhibition of growth at 96 hrs after a 48 hr washout period of GRO29A-treated U937 cells compared to U937 PBS-treated control cells. We further characterized the effect of GRO29A on leukemia cell-lines using cell cycle analysis by flow cytometry, which demonstrated apprx60% increase in S-phase cells with a concomitant decrease in G0/G1, and total loss of G2/M phase cells treated with (GRO29A) at gtoreq 1 μ M. There was also a subG0/G1 peak in U937 cells treated with (GRO29A) at gtoreq 1 μ M. **Apoptosis** was confirmed by TUNEL assay in GRO29A-treated U937 cells in time course assays with a prolonged 14% increase over PBS-treated control cells occurring 28 hours after initial GRO29A exposure. Colony formation is inhibited 100% at gtoreq 1 X 10.6 M log (GRO29A) consistent with the dose-response results. The inhibition of growth induced by GRO29A correlates with its binding to specific protein bands at the same molecular weight in all cell-lines tested by southwestern analysis. One of these bands corresponds to nucleolin antibody staining of the same blot by western analysis. Using electrophoretic mobility shift assays we detected a nuclear protein that binds specifically to GRO29A and this same nuclear protein is bound by the telomere sequence. Levels of protein binding from nuclear extracts of these leukemia cell-lines correlates with inhibition of cell growth by GRO29A. We are investigating the relationship between this inhibition of proliferation by GRO29A in these leukemia cell-lines and the ability of GRO29A to competitively inhibit nucleolin/human DNA helicase IV using helicase assays. These results provide a new therapeutic target for the treatment of leukemias.

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COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
SESSION

FULL ESTIMATED COST

218.49

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY

TOTAL
SESSION

CA SUBSCRIBER PRICE

-8.00

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